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Patients With Malignant or Potentially Malignant Ventricular Arrhythmias: Opportunities and Limitations of Drug Therapy in Prevention of Sudden Death

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Almost 90% of patients resuscitated from out of hospital cardiac arrest have coronary heart disease and can be categorized in one of three groups: acute myocardial infarction, ischemic event or primary arrhythmic event. The patients who have acute myocardial infarction have the best prognosis, and those with primary arrhythmic events have the worst. Recent studies show that ventricular arrhythmias after myocardial infarction are associated with mortality independent of any association with left ventricular dysfunction. Ventricular arrhythmias that have caused cardiac arrest or hemodynamic collapse, that is, malignant arrhythmias, should be treated aggressively and evaluated carefully with one of two methods that have high predictive accuracy for outcome: 1) the Holter recording/exercise test approach, or 2) the electrophysiologic approach.

It is not yet known whether treating potentially malignant ventricular arrhythmias after myocardial infarction with class I or III antiarrhythmic drugs will reduce mortality, but two clinical trials are under way in the United States to address this question. Beta-adrenergic blocking drugs do reduce mortality, probably as a result of both antiischemic and antiarrhythmic effects. Calcium channel blocking agents, various antiplatelet drugs and alpha-adrenergic blocking drugs are under investigation to determine their value in secondary prevention of ventricular fibrillation.

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The problem of sudden cardiac death is primarily one of malignant or potentially malignant ventricular arrhythmias in coronary heart disease. As noted elsewhere in this issue, the ventricular arrhythmias in coronary heart disease have a diverse pathophysiology. This report reviews approaches to secondary prevention of ventricular arrhythmias in patients with coronary heart disease.

Pathophysiology of Ventricular Arrhythmias

Out of Hospital Cardiac Arrest

Almost 90% of patients resuscitated from out of hospital cardiac arrest have coronary heart disease. For 20%, the cardiac arrest is the initial manifestation of heart disease. The survivors of cardiac arrest who have coronary heart disease can be categorized in three groups: those with an acute myocardial infarction, an ischemic event or primary arrhythmic event (Table 1) (1–5). Those with an acute myocardial infarction are the youngest, have the lowest prevalence of previous myocardial infarction and left ventricular dysfunction and have the best long-term survival rate. Patients with primary arrhythmic events are the oldest group, have the highest prevalence of previous myocardial infarction and left ventricular dysfunction and have the worst long-term survival rate.

Cardiac catheterization in survivors of out of hospital cardiac arrest shows a high prevalence of two or three vessel coronary artery disease and left ventricular dysfunction as judged by global left ventricular ejection fraction and wall motion abnormalities (6). Holter ambulatory electrocardiographic recordings show a high prevalence of frequent and repetitive ventricular premature depolarizations in survivors of cardiac arrest (6). Electrophysiologic studies (7–9) have demonstrated that programmed ventricular stimulation can elicit ventricular tachycardia or ventricular fibrillation in about 70% of survivors of out of hospital cardiac arrest. The likelihood of obtaining this response is greater in patients with previous myocardial infarction and pronounced left ventricular dysfunction.

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Table 1. Characteristics of Patients With Out of Hospital Cardiac Arrest

Study (first author)	Year	No. of Patients	Acute Infarction (%)	Ischemia (%)	Previous Infarction (%)	Neither Ischemia nor Infarction (%)
Liberthson (1)	1974	80	39	34	—	19
Baum (2)	1974	146	19	38	—	43
Myerberg (4)	1980	117	36		—	—
Goldstein (5)	1981	142	44	34	46	22

— = Data not given.

Malignant Ventricular Arrhythmias

A number of studies (10–12) have shown that ventricular fibrillation is overwhelmingly the most common cause of sudden cardiac death in patients with coronary heart disease. However, the pathogenetic sequences that lead to ventricular fibrillation have not yet been fully elucidated. New knowledge about these sequences will undoubtedly lead to improved secondary prevention with drugs. Clinical studies suggest that, in general, two major mechanisms of ventricular fibrillation exist in coronary heart disease: 1) myocardial ischemia and 2) scar-related ventricular tachycardia.

Ischemia. Several events produce myocardial ischemia that may lead to ventricular fibrillation: 1) increased oxygen demand in the presence of tight flow-limiting stenosis, 2) spasm of a coronary artery, usually at the site of a tight stenosis (13–15), and 3) thrombotic coronary occlusion. Lethal arrhythmias can occur at the onset of ischemia or at the time of reperfusion.

Scar-related ventricular tachycardia or fibrillation. The second common mechanism of malignant ventricular arrhythmias, scar-related ventricular tachycardia or ventricular fibrillation, usually occurs in patients with previous myocardial infarction and significant left ventricular dysfunction. Ventricular aneurysm is common in this group.

Other causes. Malignant ventricular arrhythmias can occur in other circumstances, such as presence of the congenital long QT syndrome or proarrhythmic drug effects. The latter may be associated with an acquired long QT syndrome or with marked conduction slowing in the heart.

Potentially Malignant Ventricular Arrhythmias

It has been recognized for some time that left ventricular dysfunction and ventricular arrhythmias are both potent predictors of cardiac death in patients with recent myocardial infarction. However, the relations among these three variables have been controversial. The interaction between left ventricular dysfunction and ventricular arrhythmias with respect to death holds the key to secondary preventive measures for patients with potentially malignant ventricular arrhythmias. There are two conflicting hypotheses on the relations among these three variables: 1) ventricular arrhythmias are so strongly associated with left ventricular dysfunction that they do not contribute independently to mortality, and 2) the presence of ventricular arrhythmias is a risk factor for subsequent mortality independent of any effect of left ventricular dysfunction. If the first hypothesis is true, treatment of potentially malignant ventricular arrhythmias with antiarrhythmic drugs would be irrational. If the second hypothesis is true, treatment would have a strong rationale.

Predictive role of ventricular arrhythmia versus left ventricular dysfunction. The major studies of the relations among ventricular arrhythmias, left ventricular dysfunction and mortality are summarized in Table 2. Each of the studies (16–20) used left ventricular ejection fraction and 24 hour electrocardiographic recordings to evaluate arrhythmias in postinfarction patients. Schultze et al. (16,17) studied 81 patients. Because all eight deaths in these 81 patients occurred in the subgroup that had a low ejection fraction and "complex" ventricular arrhythmias, these data cannot be informative with respect to an interaction between the two risk factors and mortality. The Multicenter Investigation of the Limitation of Infarct Size (MILIS) reported findings on 388 patients in 1982 (18) and on 533 patients in 1984 (19), and the Multicenter Post Infarction Program (MPIP) re-

Table 2. Independent Relation Among Ventricular Arrhythmia, Left Ventricular Dysfunction and Mortality After Myocardial Infarction

	Schultze (16,17)	Mukharji (18)	Bigger (20)
Year	1977	1982	1984
No. of patients	81	388	766
LVEF <40%	45 (56%)	134 (35%)	256 (33%)
"Complex" ventricular premature depolarization	29 (36%)	102 (26%)	218 (28%)
"Complex" ventricular premature depolarization and LVEF <40%	26 (32%)	47 (12%)	99 (13%)
Overall mortality	8* (10%)	25* (6%)	86† (11%)
Ventricular arrhythmias independent of left ventricular dysfunction	—	Yes	Yes

*1 year mortality rate; †2 year mortality rate. LVEF = left ventricular ejection fraction; — = not determined.

ported an analysis of 766 patients in 1984 (20). As univariate risk factors, repetitive ventricular premature depolarizations and a left ventricular ejection fraction of less than 40% predicted subsequent mortality almost equally well in the MILIS study, whereas in the MPIP study, a left ventricular ejection fraction of less than 40% was a stronger risk predictor. In both the MILIS and MPIP studies, repetitive ventricular premature depolarizations were strongly related to mortality after adjusting for left ventricular dysfunction with a left ventricular ejection fraction of less than 40%. Because the risk of dying in the years after myocardial infarction is independently increased by left ventricular dysfunction and ventricular arrhythmias, these two factors can be multiplied to give the overall risk of death during follow-up study.

Secondary Prevention With Drug Treatment

Malignant Ventricular Arrhythmias

There is a strong consensus that malignant ventricular arrhythmias should be treated vigorously and nonempirically. Drugs must be selected and evaluated using rigorous methodology. Two methods have been shown capable of predicting a good outcome: 1) a noninvasive approach using Holter electrocardiographic recordings and exercise testing (21), and 2) an electrophysiologic approach using programmed ventricular stimulation to evaluate treatment (22–25). The protocols for these two methods has been reviewed elsewhere (26). Both methods are complex, require a high level of expertise and are time-consuming and expensive. There has been no direct comparison of the two methods so that a preference cannot be stated in most cases. When ventricular tachycardia occurs frequently but does not cause severe hemodynamic effects, the Holter recording exercise test approach is preferable. When the frequency of sustained ventricular tachycardia is low and its hemodynamic effects are devastating, the electrophysiologic approach is superior.

Holter recording/exercise test method. Only one group (21) has reported the long-term outcome of patients with malignant ventricular arrhythmias who were managed using the Holter recording/exercise test approach (Table 3). The probability of death during 3 years of follow-up was much greater in the patients whose unsustained ventricular tachycardia could not be completely suppressed.

Electrophysiologic method. Several groups have reported on the ability of programmed ventricular stimulation to guide drug therapy. As an example, in the study of Swerdlow et al. (27) (Table 3), the end point for judging drug effectiveness was a change from sustained ventricular tachycardia or ventricular fibrillation to less than five repetitive ventricular responses in response to programmed ventricular stimulation. The risk of death in drug nonresponders was eight times greater than for drug responders. This result is not significantly different from that obtained with the Holter recording/exercise test approach.

Table 3. Outcome of Two Treatment Programs for Malignant Ventricular Arrhythmias

Method of Arrhythmia Control	Drug Responders		Drug Nonresponders	
	No.	Mortality Rate*	No.	Mortality Rate*
Holter monitor/ exercise test (21)	98	14%	25	84%
Electrophysiologic (27)	103	20%	102	68%

*Approximate 3 year mortality rate.

Because there is no controlled comparison with an untreated group, we cannot attribute the improved survivorship in patients who respond to drug therapy to a drug effect. It is possible that drug response can predict outcome without directly influencing it. The question of causality between treatment and response is not a trivial one. If treatment does not influence outcome, short-term treatment would be useful for classifying patients, but long-term treatment would merely expose patients to the risk of adverse drug effects for no benefit. Controlled trials of treatment for malignant ventricular arrhythmias are difficult but not impossible to design. With such trials, additional information will be forthcoming to define the effect of treatment on subsequent mortality.

Class I Antiarrhythmic Drugs for Potentially Malignant Ventricular Arrhythmias

With recent studies (18–20) clearly showing that potentially malignant ventricular arrhythmias are independent predictors of mortality, there is a strong rationale for treating ventricular arrhythmias in the first year after myocardial infarction. The next question is: Will reducing potentially malignant ventricular arrhythmias significantly reduce mortality? Clearly, we do not know the answer to this question. Two major studies are underway to address this question: the Cardiac Arrhythmia Pilot Study (CAPS) and the Timolol, Encainide, Sotolol Trial (TEST).

Cardiac Arrhythmia Pilot Study (CAPS). This study was initiated during the summer of 1983 in 10 centers in the United States and Canada to determine whether a treatment strategy could be identified that would provide effective control of potentially malignant ventricular arrhythmias with an acceptable level of adverse effects. Patients are enrolled 6 to 60 days after myocardial infarction if they have the qualifying arrhythmias, either an average of 10 or more ventricular premature depolarizations per hour for 24 hours or 5 or more episodes of nonsustained ventricular tachycardia per day. Eligible patients are randomly assigned to one of five treatment tracks; four tracks provide active an-

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tiarrhythmic drug treatment sequences and one track provides placebo treatment. Dose adjustment and drug changes are permitted within the active treatment tracks. The drugs used in CAPS are encainide, ethmozin, flecainide and imipramine. In CAPS, efficacy is defined as a 70% reduction in ventricular premature depolarization frequency and a 90% reduction in runs of ventricular premature depolarizations. If an effective, safe treatment strategy is identified in CAPS, a fullscale trial will be considered as a second stage.

Timolol, Encainide, Sotolol Trial (TEST). The 10 TEST hospitals started enrolling postinfarction patients in the winter of 1984 to determine whether treatment of patients with both potentially malignant ventricular arrhythmias and left ventricular dysfunction (ejection fraction <40%) can reduce total cardiac mortality and sudden cardiac death. Patients are enrolled 6 to 28 days after myocardial infarction. To be eligible for TEST, patients must have an average of 10 or more ventricular premature depolarizations per hour or unsustained ventricular tachycardia as well as a left ventricular ejection fraction of less than 40%. Patients are randomly assigned to treatment with one of three drugs: timolol, 10 mg twice a day; encainide, 50 mg twice a day or sotolol, 320 mg twice a day. Treatment will be evaluated by 24 hour electrocardiographic recordings and overall benefit judged by effect on mortality. TEST will last 3 years and plans to enroll 900 patients.

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